Preventive Medicine 89 (2016) 200–206

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Role of renal function in cardiovascular risk assessment: A retrospective cohort study in a population with low incidence of coronary heart disease

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ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form 18 May 2016
Accepted 5 June 2016
Available online 7 June 2016

Keywords:
Primary care
Cardiovascular risk assessment
Glomerular filtration rate
Electronic medical records

ABSTRACT

Background. Early-stage chronic kidney disease (CKD), a marker of cardiovascular risk, is susceptible to therapeutic intervention but need further study in populations with low incidence of coronary heart disease (CHD). Incorporating glomerular filtration rate (GFR) could improve cardiovascular risk prediction in these patients.

Objective. To determine if decreased GFR is associated with increased risk of cardiovascular morbidity and all-cause mortality and to analyse GFR effect on cardiovascular risk prediction in a population with low CHD incidence.

Methods. Retrospective, observational, population-based study of 1,081,865 adults (35–74 years old). Main exposure variable: GFR. Outcomes: CHD, cerebrovascular disease, cardiovascular diseases, all-cause mortality. Association between GFR categories of CKD (G1–G5) and outcomes was tested with Cox survival models. G1 was defined as the reference category. Predictive value of GFR was evaluated by integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices.

Results. Beginning at stage-3a CKD, increased risk was observed for coronary (HR 1.27 (95%CI 1.14–1.43)), cerebrovascular (HR 1.19 (95%CI 1.06–1.34)), cardiovascular (HR 1.23 (95%CI 1.13–1.34)) and all-cause mortality risk (HR 1.17 (95%CI 1.07–1.27)). GFR did not increase discrimination and reclassification indices significantly for any outcome.

Conclusion. In general population with low CHD incidence and stage-3 CKD, impaired GFR was associated with increased risk of all cardiovascular diseases studied and all-cause mortality, but adding GFR values did not improve cardiovascular risk calculation. Despite a four-fold higher rate of CHD incidence at GFR G3a compared to G1, this represents moderate cardiovascular risk in our context.

1. Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity worldwide. They account for 30% of global mortality and are expected to remain the leading cause of death in coming years (World Health Organization, 2011) (Mathers & Loncar, 2006). Although southern Europe has one of the lowest cardiovascular mortality and morbidity rates in the European Union (Nichols et al., 2012), these diseases constitute one of the main morbidity impacts, being the second leading cause of expected years of life lost and the first cause of hospitalization (INE, 2014) (Gènova-Maleras et al., 2011). Therefore, prevention of cardiovascular diseases remains a priority of health policies and biomedical research in this population.

Currently, one of the main disease prevention strategies is to intervene in the high-risk healthy population. Treating cardiovascular risk factors decreases the risk of cardiovascular diseases (Graham et al., 2007). Although risk functions are used to identify those individuals at higher risk, the functions are not sufficiently accurate (Marrugat et al.,

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http://dx.doi.org/10.1016/j.ypmed.2016.06.004

2007). Therefore, it is necessary to improve the predictive ability of risk functions by considering new risk factors.

Recently, several studies have shown that impaired renal function, even at very early stages, is independently associated with the occurrence of cardiovascular events (Go et al., 2004) (Brugts et al., 2005) (Meisinger et al., 2006) (Van Biesen et al., 2007) (Di Angelantonio et al., 2007) (Astor et al., 2008) (Cirillo et al., 2008) (Matsushita et al., 2010b). Thus, current clinical practice guidelines recommend maximizing cardiovascular prevention in patients with chronic kidney disease (CKD) at all stages (Group KDIGO (KDIGO) CW, 2013) (Bover-Sanjuán et al., 2014) (Rabar et al., 2014 Jan). Moreover, recent research has suggested that markers of CKD would help to improve the prediction of cardiovascular events in addition to traditional cardiovascular risk factors in populations with high cardiovascular risk (Di Angelantonio et al., 2010) (Shara et al., 2011) (Smink et al., 2012). Nonetheless, studies on the role of impaired renal function as a cardiovascular risk are mainly carried out in populations with high incidence of CHD. In this study, we aimed to examine the potential capacity of CKD, as defined by glomerular filtration rate (GFR), to improve the prediction of cardiovascular events and all-cause mortality in a general population with low incidence of CHD (Marrugat et al., 2011).

2. Materials and methods

2.1. Study design

2.1.1. Retrospective cohort study

2.1.1.1. Data source. Data were obtained from the Information System for the Development of Research in Primary Care (SIDIAP). This clinical database contains the anonymized, longitudinal medical records of nearly five million patients, comprising around 80% of the Catalan and 10.2% of the Spanish populations (Bolíbar et al., 2012). The records contain demographic information, clinical diagnoses (International Classification of Diseases 10th revision [ICD-10]), referral and hospital discharge information (International Classification of Diseases 9th revision [ICD-9]), laboratory tests and treatments (drug prescriptions and drugs invoiced at the community pharmacy). General practitioners follow regulated protocols on data recording, and are assessed for its completeness and continuity: the records qualified as "up to standard" for biomedical research are called SIDIAP^{Q} (García-Gil et al., 2011) and were used in the present study. The quality of SIDIAP data has been previously documented, and the database has been widely used to study the epidemiology of a number of health outcomes (Ramos et al., 2012) (Prieto-Alhambra et al., 2014) (Vinagre et al., 2012) (Simó et al., 2013) (Violán et al., 2013). This study received its approval from the research ethics committee of IDIAP Jordi Gol.

2.2. Participants

In total, 1,081,865 people aged 35 to 74 years without previous history of cardiovascular disease, defined as myocardial infarction (MI), angina pectoris, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD), and who were registered with a primary health care centre providing data to SIDIAP^{Q} between January 2008 and December 2013, were eligible for inclusion in this study.

2.2.1. Follow-up and outcomes

The six-year study period was January 2008 to December 2013. The follow-up period was defined from January 2009 to 2013. For individuals with a creatinine measurement, we used the first record as an index date; without creatinine data, January 2009 was the index date. Baseline period was defined as 1-year before the index date.

Patients were censored at the earliest date of the diagnosis of interest, at transfer out of the primary health care centre or at the study end date (31 December, 2013). Time to first event was considered for all analyses.

Vascular diseases were identified in follow-up from relevant SIDIAP^{Q} codes in the patients' clinical files, both primary care and hospital discharge records. The cardiovascular codes have been previously validated in SIDIAP (Ramos et al., 2012).

The primary outcomes were *coronary heart disease*, a composite of myocardial infarction (MI) and angina; *cerebrovascular disease*, consisting of stroke and transient ischemic attack (TIA); *cardiovascular diseases*, a composite of MI, angina, stroke and TIA; and finally, *all-cause mortality*.

The presence of vascular disease was defined according to the following criteria:

- Coronary heart disease: MI (ICD-10 codes: I21-I23 and subcategories; ICD-9 code: 410) and angina (ICD-10 codes: I20 and subcategories; ICD-9: 411.1, 413); and
- Cerebrovascular disease: stroke (ICD-10 codes: I61-I64 and subcategories; ICD-9: 433, except for non-occlusive disease, so 433.00, 433.10, 433.20, 433.30, 433.80, 433.82, 433.90, 434.00, 434.10, 434.11, 434.90) and TIA (ICD-10 codes: G45-G46; ICD-9 code: 435).

2.2.2. Main exposure

- Standardized creatinine was used for CKD-Epidemiology Collaboration (CKD-EPI) calculations, according to "Kidney disease: Improving global outcomes" (KDIGO) guidelines (Group KDIGO (KDIGO) CW, 2013) (mg/dl).
  - o Glomerular filtration rate (GFR) was calculated by CKD-EPI equation (Levey et al., 2009).
  - o GFR categories in CKD were defined by the KDIGO guideline (Group KDIGO (KDIGO) CW, 2013):
    - G1 ≥ 90 ml/min/1.73 m^2
    - G2 60–89 ml/min/1.73 m^2
    - G3a 45–59 ml/min/1.73 m^2
    - G3b 30–44 ml/min/1.73 m^2
    - G4 15–29 ml/min/1.73 m^2
    - G5 < 15 ml/min/1.73 m^2.

2.2.3. Covariates

A set of variables were defined a priori and obtained from SIDIAP^{Q} at baseline:

- Age
- Sex
- Hypertension (yes/no) or record of antihypertensive drug invoicing
- Dyslipidaemia (yes/no)
- Smoking (yes/no)
- Obesity (yes/no) defined as BMI > 30 kg/m^2
- Diabetes (yes/no) or record of antidiabetic drug invoicing
- Systolic blood pressure (SBP) (mm Hg)
- Diastolic blood pressure (DBP) (mm Hg)
- Laboratory tests: fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides
- Body mass index (BMI) (kg/m^2)
- Drug use: antihypertensive agents, antidiabetic agents, or statins and other lipid-lowering drugs
- Ten-year CHD risk, estimated using the Framingham function adapted and validated in the Spanish population by the REGICOR study (Marrugat et al., 2007).

2.3. Statistical analysis

Categorical variables are presented as percentages and continuous variables as mean (standard deviation) and 95% confidence intervals (95%CI) were calculated when required.

Missing data were imputed using 20 multiple imputations by chained equations (White et al., 2011) to replace baseline missing values in the logarithm of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, systolic blood pressure and the difference between systolic and diastolic blood pressure, weight, height and creatinine. We also performed a case-complete sensitivity analysis to assess the proper functioning of the multiple imputation process. The association between GFR and cardiovascular events/all-cause mortality was assessed by multivariate Cox survival models adjusted for age, sex, smoking habit, diabetes, blood pressure levels, total cholesterol and, HDL cholesterol levels. GFR ≥ 90 ml/min/1.73 m^2 (category G1) was defined as the reference value. We tested the proportional hazards assumption and analysed linearity between GFR and all outcomes.

We calculated Harrell's C index to assess the discrimination for censored time-to-event data and reclassification measures to assess the prediction of risk for all outcomes with GFR: Integrated discrimination improvement index (IDI) in continuous form and net reclassification improvement index (NRI) calculated at five years. Bootstrap estimation was performed to calculate 95% confidence intervals of the NRI.

Models for CHD and cardiovascular disease without angina were also built to assess the possible diluting effect of angina. Sensitivity analysis with models defining CKD only as GFR < 60 ml/min/1.73 m^2 were also performed.

We used R-package (version 3.2) and the survidinri and nricens packages (Team R Core, 2014) for statistical analyses, with two-sided tests and $p < 0.05$.

3. Results

3.1. Baseline results

In total, 1,081,865 primary care patients aged 35–74 years were included between 2008 and 2013. In more than 75% of patients, follow-up was 5 years.

Table 1 presents overall baseline characteristics of the study population according to GFR categories of CKD and the percentage of missing values for the imputed variables. The percentage of missing values for weight, height and glucose were 44.7%, 46.1%, and 53.6%, respectively. These variables are not presented in Table 1 but were used in the multiple imputation process. The mean age was 49.5 (11.6) years, and women constituted 51% of the cohort. Diabetes was present in about 7% of participants, obesity in 31%, hypercholesterolemia in 20% and hypertension in 21%; about one third were smokers. Mean 10-year coronary risk was 3%. The most frequently prescribed medications were antihypertensive agents (15.7%), followed by statins (9.3%), antidiabetic agents (4.5%), and aspirin (2.7%). In general, the proportion of all these factors increased as GFR decreased, apart from patients in GFR category G5. Mean GFR was 95 ml/min/1.73 m^2 (SD: 16.1). However, the distribution was skewed and 1,057,283 patients in GFR categories G1 and G2 accounted for nearly 97% of the total population. There were 24,582 (2.2%) participants with a GFR below 60 ml/min/1.73 m^2; 20,465 (83%) of them belonged to GFR category G3a.

The proportion of missing data in the variables considered for the risk function prediction and a comparison of the complete-case dataset and imputed dataset are shown in the Supplementary file (Tables S1–S3). Mean values of these variables remained similar after multiple imputations.

3.2. Outcome incidences

Within the period 2009–2013, overall unadjusted incidences per 100,000 persons-year at risk (PYAR) of coronary heart disease, cerebrovascular disease, cardiovascular diseases and all-cause mortality were 205.1 (95%CI 201.1–209.1), 182.0 (95%CI 178.2–185.7), 381.2 (95%CI 375.7–386.7) and 264.0 (95%CI 259.4–268.5), respectively. The risks increased with stage of renal function, except that individuals in stage 5 had a lower incidence of stroke (Table 2).

3.3. Multivariate associations

Adjusted hazard ratios significantly differed between GFR categories (CKD) for coronary heart disease, cerebrovascular disease, cardiovascular diseases and all-cause mortality (Fig. 1). Patients with lower GFR were more likely to have higher incidence of coronary and cerebrovascular events and higher all-cause mortality. Hazards ratios ranged from 1.07 (95%CI 1.01–1.14) to 3.02 (95%CI 1.51–6.07) for coronary heart disease, 1.02 (95%CI 0.96–1.09) to 2.06 (95%CI 0.92–4.59) for cerebrovascular disease, 1.05 (95%CI 1.00–1.09) to 2.58 (95% 1.52–4.36) for

Table 1
Baseline characteristics of the study population by glomerular filtration rate categories.

			Glomerular filtration rate categories in chronic kidney disease					
Characteristics	Total	% missing	G1	G2	G3a	G3b	G4	G5
Population[a]	1,081,865 (100%)	–	703,242 (65.00%)	354,041 (32.73%)	20,465 (1.89%)	3447 (0.32%)	475 (0.04%)	195 (0.02%)
Age[b] (years)	49.53 (11.6)	–	45.90 (9.7)	55.71 (11.9)	63.87 (9.7)	66.14 (8.5)	64.75 (10.0)	60.37 (11.1)
Sex[a] (women)	550,712 (50.9%)	–	364,001 (51.8%)	173,954 (49.1%)	10,740 (52.5%)	1689 (49.0%)	240 (50.5%)	90 (46.2%)
Hypertension[a]	226,901 (21.0%)	–	94,823 (13.5%)	115,799 (32.7%)	12,679 (62.0%)	3006 (87.2%)	425 (89.6%)	167 (85.6%)
Dyslipidemia[a]	219,971 (20.3%)	–	108,332 (15.4%)	100,944 (28.5%)	8625 (42.2%)	1749 (50.8%)	232 (49.0%)	87 (44.6%)
Smoking[a]	371,229 (34.3%)	–	254,443 (36.2%)	109,937 (31.1%)	5519 (27.0%)	1094 (31.7%)	161 (33.9%)	73 (37.4%)
Obesity[a]	330,525 (30.6%)	–	198,697 (28.3%)	120,980 (34.2%)	8803 (43.0%)	1730 (50.2%)	242 (50.9%)	72 (37.1%)
Diabetes[a]	74,725 (6.9%)	–	35,916 (5.1%)	33,986 (9.6%)	3600 (17.6%)	1019 (29.6%)	147 (31.0%)	54 (27.7%)
Systolic blood pressure (mmHg)[b]	127.55 (16.6)	64.1%	126.10 (16.3)	130.01 (16.7)	133.51 (17.1)	135.35 (18.3)	135.51 (19.3)	136.23 (25.0)
Diastolic blood pressure (mmHg)[b]	77.23 (9.9)	64.5%	76.97 (10.0)	77.72 (9.8)	77.77 (9.8)	77.39 (10.5)	76.65 (11.1)	77.65 (13.5)
Cholesterol (mg/dL)[b]	205.56 (38.5)	54.3%	203.21 (38.3)	210.00 (38.5)	210.23 (39.2)	202.81 (40.7)	198.32 (46.1)	179.83 (47.6)
HDL cholesterol (mg/dL)[b]	54.75 (14.8)	66.6%	54.59 (14.8)	55.13 (14.9)	54.59 (14.8)	51.51 (14.3)	48.95 (13.5)	48.69 (14.1)
LDL cholesterol (mg/dL)[b]	127.15 (34.1)	67.3%	125.49 (33.9)	130.39 (34.2)	129.25 (34.7)	121.61 (35.0)	118.19 (37.6)	105.38 (38.2)
Triglycerides (mg/dL)[b]	121.50 (78.9)	64.9%	118.77 (79.2)	125.72 (77.5)	135.79 (80.5)	152.63 (91.7)	163.32 (110.0)	143.93 (86.8)
Body mass index (kg/m^2)[b]	27.48 (5.0)	47.7%	27.15 (5.0)	28.00 (4.9)	29.09 (5.1)	29.81 (5.2)	29.89 (5.6)	28.30 (4.9)
Statins[c]	100,291 (9.3%)	–	39,443 (5.6%)	53,259 (15.0%)	5869 (28.7%)	1411 (40.9%)	222 (46.7%)	85 (43.6%)
Aspirin[c]	29,223 (2.7%)	–	10,681 (1.5%)	15,881 (4.5%)	1987 (9.7%)	557 (16.2%)	83 (17.5%)	32 (16.4%)
Antihypertensives[c]	169,546 (15.7%)	–	64,129 (9.1%)	91,452 (25.8%)	10,828 (52.9%)	2642 (76.7%)	367 (77.4%)	126 (64.6%)
Antidiabetic agents[c]	49,143 (4.5%)	–	22,610 (3.2%)	23,104 (6.5%)	2552 (12.5%)	744 (21.6%)	97 (20.6%)	34 (17.4%)
Creatinine (mg/dL)[b]	0.83 (0.2)	66.4%	0.75 (0.1)	0.95 (0.2)	1.21 (0.2)	1.60 (0.3)	2.42 (0.6)	6.33 (2.6)
GFR (ml/min/1.73 m^2)[b]	95.08 (16.1)	–	104.60 (8.9)	79.17 (7.8)	54.83 (4.0)	39.38 (4.1)	24.61 (4.3)	9.06 (3.4)
10-year coronary risk	3.14 (3.2)		2.54%	4.14%	5.58%	6.78%	6.68%	5.39%

[a] N and %.
[b] Mean and standard deviation.
[c] Drug consumption, N and %.

Table 2
Number of events and incidence rates per 100,000 participants/year (95% CI) for each outcome by GFR category in chronic kidney disease.

Outcomes	Total events Incidence/100,000/yr (95% CI)	GFR categories in chronic kidney disease					
		G1	G2	G3a	G3b	G4	G5
Coronary heart disease[a]	10,031	4445	4924	517	123	15	8
	205.1	141.2	301.7	555.3	833.3	820.8	1206.3
	(201.1–209.1)	(136.4–146.0)	(292.1–311.4)	(498.8–611.7)	(655.7–1010.8)	(380.2–1261.5)	(370.4–2042.3)
Cerebrovascular disease[b]	8900	3522	4697	531	124	21	6
	182.0	111.8	287.7	570.0	845.1	1126.3	900.1
	(178.2–185.7)	(107.6–116.1)	(278.3–297.1)	(510.9–629.1)	(675.3–1014.8)	(606.5–1646.0)	(179.9–1620.3)
Cardiovascular disease[c]	18,634	7871	9452	1023	238	36	14
	381.2	250.1	579.5	1101.3	1619.5	1940	2113.3
	(375.7–386.7)	(243.8–256.4)	(566.2–592.9)	(1016.4–1186.3)	(1385.4–1853.6)	(1277.6–2602.6)	(1006.3–3220.2)
All-cause mortality	12,917	5692	6135	728	276	62	24
	264.0	180.7	375.6	780.8	1874.3	3349.9	3596.7
	(259.4–268.5)	(175.2–186.2)	(364.1–387.2)	(715.8–845.8)	(1623.9–2124.7)	(2464.8–4235.0)	(2157.7–5035.7)

Values in each cell: 1. number of events. 2 incidence rate per 100,000 participants. 3.95% CI (confidence interval) of the incidence rate.
[a] Acute myocardial infarction and angina.
[b] Stroke and transient ischemic attack.
[c] Myocardial infarction, angina, stroke and transient ischemic attack.

cardiovascular diseases and 0.91 (95%CI 0.86–0.97) to 5.26 (95%CI 3.51–7.86) for all-cause mortality. From the GFR category G3a upwards, the increase in risk was significant for all outcomes –, coronary heart disease (HR 1.27 (95%CI 1.14–1.43)), cerebrovascular disease (HR 1.19 (95%CI 1.06–1.34)), cardiovascular diseases (HR 1.23(95%CI 1.13–1.34)), and all-cause mortality (HR 1.17 (95%CI 1.07–1.27)). Models without angina showed no relevant differences compared to the models including this outcome (data not shown).

3.4. Discrimination and reclassification measures with glomerular filtration rate

GFR did not increase the NRI index significantly in any outcome: coronary heart disease (NRI 0.3%, 95%CI −0.45–1.11), cerebrovascular disease (NRI 0.2%, 95%CI −0.63–1.04), cardiovascular diseases (NRI −0.005%, 95%CI −0.46–0.45) and all-cause mortality (NRI 0.03%,

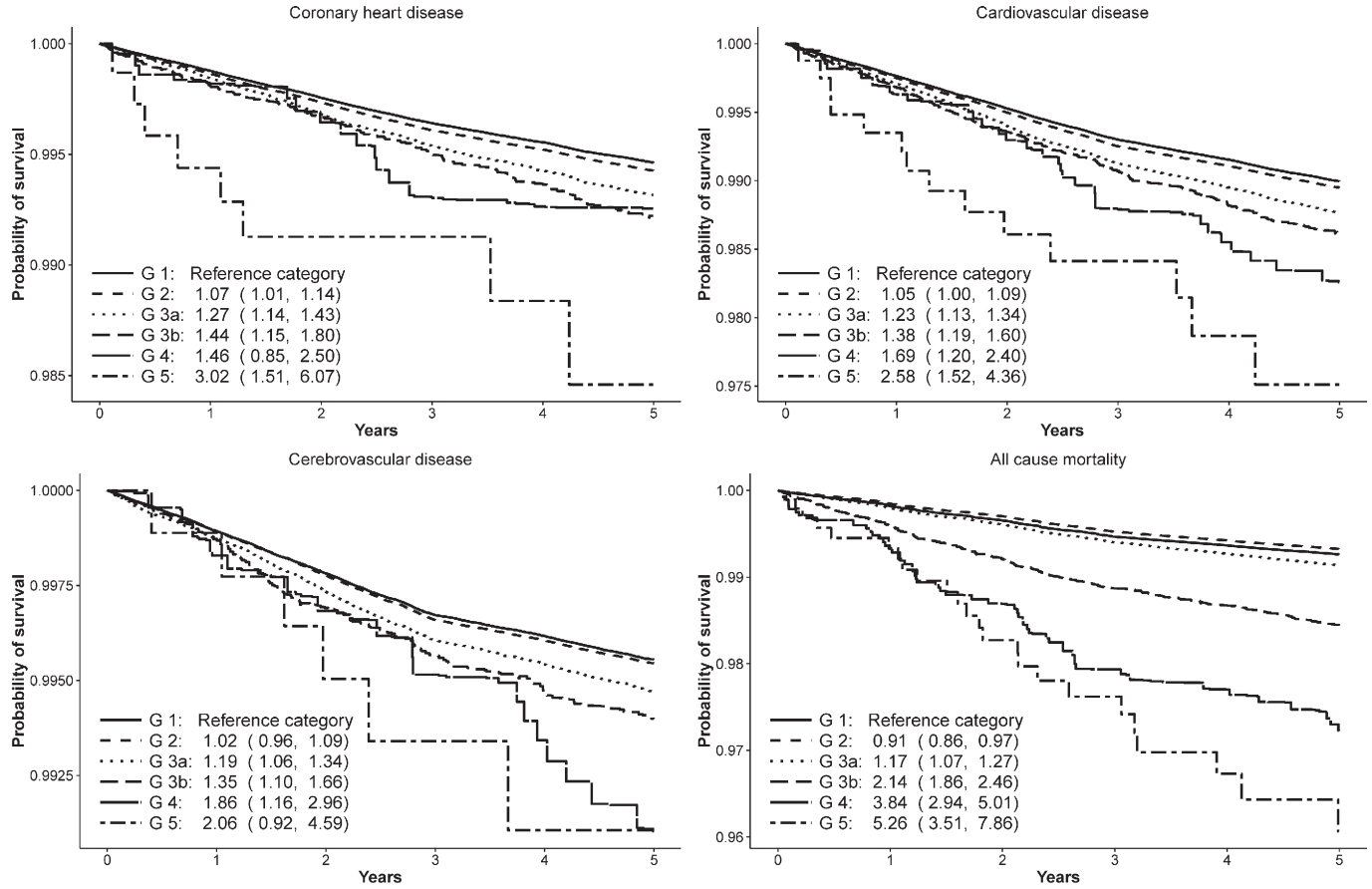

Fig. 1. Multivariate Cox survival models. Models adjusted for: age, sex, smoking habit, diabetes, blood pressure levels, total cholesterol and HDL cholesterol levels. Trend test p-value < 0.002 in all outcomes.

95%CI −0.00–0.94 (Table 3). A sensitivity analysis that defined CKD only as GFR < 60 ml/min/1.73 m^2 instead of the GFR categories of CKD stages produced similar results (data not shown).

4. Discussion

The present study in a general population without previous cardiovascular disease and with low incidence of coronary disease shows that impaired levels of GFR are associated with an increased incidence of cardiovascular events and all-cause mortality. Risk of suffering either coronary or cerebrovascular events was clinically significant higher beginning at GFR category G3a, the level that defines CKD onset. However, including GFR did not improve the predictive ability of cardiovascular risk functions.

In relation to coronary events, previous studies in populations with low cardiovascular risk showed similar results. Cirillo et al. (Cirillo et al., 2008) found an increased cardiovascular risk with an impaired GFR from GFR category G3a upwards. As expected, the magnitude of this association was lower than that found in populations with higher cardiovascular risk (Di Angelantonio et al., 2010).

Our findings on cerebrovascular events are consistent with a recent meta-analysis (Lee et al., 2010) examining the association between impaired GFR (G3a and higher) and the incidence of cerebrovascular disease.

For all-cause mortality, our findings suggested significantly increased risk for patients in GFR category G3a, which was also reported by Matsushita et al. (Matsushita et al., 2010b). However, they reported a greater magnitude of the association. In our study, GFR category G2 was more likely to be protective for all-cause mortality. It is possible, however, that some individuals might have been misclassified as G2 (>60 ml/min/1.73 m^2) and the finding may be not reliable due to the CKD-EPI equation's lack of precision in GFR estimation (Levey et al., 2009; Matsushita et al., 2010a).

Most of the current international guidelines consider patients with CKD to be at high risk of cardiovascular events and death, independent of their estimated cardiovascular risk and, consequently, recommend reducing the goals for other cardiovascular risk factors when evaluating these individuals (Perk et al., 2012; Group KDIGO (KDIGO) CW, 2013; (Rabar et al., 2014). Nonetheless, this recommendation would apply only in populations with an observed incidence of CHD higher than the risk thresholds for high coronary risk, as defined in international guidelines.

Thus, recommendations of these guidelines may be adequate in countries with high incidence of CHD or cardiovascular mortality (Shara et al., 2011; Astor et al., 2008; Hallan et al., 2006), whereas it may be less suitable in low-incidence populations (Cirillo et al., 2008; Wen et al., 2008; Nakayama et al., 2007) and, particularly, in patients with moderate renal impairment.

In our study, despite a four-fold higher incidence rate of CHD at GFR category G3a, compared to G1, it remained close to 0.55% annually (i.e., 5.5% at 10 years), which is a moderate level of cardiovascular risk. Additionally, moderate renal impairment (GFR category G3a) was observed in more than 80% of patients with GFR below 60 ml/min/1.73 m^2. Finally, we observed that the classical cardiovascular risk factors accounted for most of the individual CHD risk in GFR category G3a, compared to G1, as only 27% was associated to GFR ((unadjusted HR 3.95 (95% CI: 3.55–4.41), adjusted HR 1.27 (95% CI: 1.14–1.43)).

Thus, to consider all CKD patients at high cardiovascular risk, especially patients with moderate CKD, may result in an overestimation of their risk and could lead to unnecessary interventions. Individuals from a population with a low incidence of CHD and with impaired GFR should not automatically be considered at high cardiovascular risk.

Incorporating information on renal impairment into risk assessment tools was one possible option to improve the assessment of cardiovascular risk in patients with CKD. As we observed, however, this change did not significantly improve risk function performance. This finding is consistent with previous literature (Di Angelantonio et al., 2010; Shara et al., 2011; Smink et al., 2012; Donfrancesco et al., 2013; Puddu et al., 2014). Therefore, the main concern remains finding the best way to deal with the excess of risk in this population in the clinical practice. One strategy could be to take GFR information into account in individuals with borderline (Regicor 8–9% or Score 3–4%) cardiovascular risk (Conroy et al., 2003) in order to reclassify them more accurately when assessing their individual risk. Some prevention guidelines (Perk et al., 2012) recommend this strategy to account for other risk factors, such as sedentary behaviour or family history of premature cardiovascular disease, as a part of the decision-making process in clinical practice.

4.1. Strengths and limitations

A major strength of this study is that it was based on validated, high-quality, electronic medical records that provided a large sample size and reflected real-life conditions. Instead of excluding individuals with missing data, we chose to use multiple imputation of the missing values for continuous variables. This method intends to avoid selection bias if the population with missing data somehow differs from those with complete data (White et al., 2011).

Albuminuria and uric acid are also predictors of all-cause and cardiovascular mortality and atherosclerosis (Puddu et al., 2014; Sambon et al., 2012; Krishnan et al., 2011). However, we were unable to fully examine the renal function because we could not get albuminuria and uric acid data. These screening tests are performed only in certain clinical conditions such as diabetes or hypertension. Moreover, data from

Table 3
Measures of discrimination and reclassification for each model.

		Discrimination and reclassification measures		
Outcomes	C-index model 1 (95% CI)[a]	C-index model 2 (95% CI)[b]	IDI (%) (95% CI)	NRI (%) (95% CI)
Coronary heart disease[c]	0.8003 (0.7945–0.8061)	0.8007 (0.7949–0.8065)	0.0201 (−0.0067–0.0469)	0.3289 (−0.4590–1.1165)
Cerebrovascular disease[d]	0.8070 (0.8010–0.8131)	0.8074 (0.8013–0.8134)	0.0090 (−0.0071–0.0251)	0.2042 (−0.6342–1.0426)
Cardiovascular disease[e]	0.7975 (0.7933–0.8017)	0.7979 (0.7937–0.8021)	0.0269 (0.0005–0.0532)	−0.0052 (−0.4609–0.4506)
All-cause mortality	0.7866 (0.7816–0.7916)	0.7878 (0.7824–0.7924)	0.1502 (0.0146–0.2859)	0.0390 (−0.0087–0.9441)

CI: Confidence interval.
[a] Model 1: Adjusted for age, sex, smoking habit, diabetes, blood pressure levels, total cholesterol and HDL cholesterol.
[b] Model 2: Model 1 plus glomerular filtration rate.
[c] Acute myocardial infarction and angina.
[d] Stroke and transient ischemic attack.
[e] Myocardial infarction, angina, stroke and transient ischemic attack.

other more accurate methods for estimating GFR, such as Cystatin C measurement (Coll et al., 2000) were not available. However, our aim was to find a kidney function marker for improving cardiovascular risk assessment in the general population, and these methods are not easily accessible in primary care. Therefore, GFR estimated by the CKD-EPI equation is a more suitable measurement for this purpose than albuminuria or GFR measured by Cystatin C. We could not use a race variable to calculate GFR; however, Caucasian race is predominant in our population, and thus we assume that this limitation does not modify our findings. We were also unable to analyse the effect of renal function on cardiovascular death, as cause of death information is not available in the SIDIAP database. Although GFR estimation is not recommended in pregnant women, individuals with acute renal failure, or type 1 diabetes (Perrone et al., 1992; Rule & Teo, 2009), these individuals were not excluded from our study. Nonetheless, it is unlikely that their GFR estimation had a major impact on our results as these individuals represented less than 1% of the total population. The relationship between GFR and the outcomes was non-linear. Although arbitrary categorisations (e.g., quartiles, dichotomisation) may not accurately describe non-linear relationships, categories defined according to KDIGO guidelines have been validated/are appropriate for use in CVD risk management (Group KDIGO (KDIGO) CW, 2013).

5. Conclusion

In general population with low incidence of CHD and CKD stage 3a or higher, impaired GFR implies an increased risk of cardiovascular diseases, both coronary and cerebrovascular, as well as an increased risk of all-cause mortality. However, the addition of GFR in a cardiovascular risk model did not improve prediction. Despite a four-fold higher incidence rate of CHD at GFR category G3a, compared to G1, it remained close to 0.55% annually (i.e., 5.5% at 10 years), which is a moderate cardiovascular risk in our context. Thus, individuals with impaired GFR from a population with a low incidence of CHD should not automatically be considered at high cardiovascular risk.

Funding

This project was supported by grants from the Spanish Government's 2011 Health Ministry call for clinical research proposals (EC11-349), the 2012 Ministry of Science and Innovation call through the Carlos III Health Institute (Net RD12/0005/0002), and the 2013 call from the Carlos III Health Institute for clinical research proposals related to the Health Strategic Action Plan, 2013–2016, under the Program on Research Related to Society's Challenges, within the framework of Spain's 2013–2016 Plan for Scientific and Technical Research and Innovation (PI13/01,511, co-funded by the European Fund for Regional Development (EFRD) of the European Union). Additional funding was provided by the 2012 IDIAP Jordi Gol scholarship call (9è *ajut a l'impuls d'estratègies de recerca a l'atenció primària mitjançant la intensificació d'investigadors*). M.G. is funded by a FEDER contract from Carlos III Health institute (FIS CP12/03287).

Conflict of interest

The authors declare that they have no conflict of interest.

Transparency document

The Transparency document related to this article can be found in the online version.

Acknowledgments

We thank Elaine Lilly, Ph.D., of Writer's First Aid for her feedback on English language usage.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2016.06.004.

References

Astor, B.C., Hallan, S.I., Miller, E.R., Yeung, E., Coresh, J., 2008 May 15. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. Am. J. Epidemiol. [Internet] 167 (10), 1226–1234 [cited 2012 Oct 24].

Bolíbar, B., Fina Avilés, F., Morros, R., del M, G.-G.M., Hermosilla, E., Ramos, R., et al., 2012 May 19. [SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research]. Med. Clin. (Barc) [Internet] 138 (14), 617–621 [cited 2014 Oct 7].

Bover-Sanjuán, J., Cebollada, J., Escalada, J., Esmatjes, E., Fácila, L., Gamarra, J., et al., 2014. Consensus document for the detection and management of chronic kidney disease. Nefrologia [Internet] 34 (2), 243–262.

Brugts, J.J., Knetsch, A.M., Mattace-Raso, F.U.S., Hofman, A., Witteman, J.C.M., 2005. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam Study. Arch. Intern. Med. [Internet] 165 (22), 2659–2665 [cited 2012 Nov 22].

Cirillo, M., Lanti, M.P., Menotti, A., Laurenzi, M., Mancini, M., Zanchetti, A., et al., 2008 Mar 24. Definition of kidney dysfunction as a cardiovascular risk factor: use of urinary albumin excretion and estimated glomerular filtration rate. Arch. Intern. Med. [Internet] 168 (6), 617–624 [cited 2012 Nov 22].

Coll, E., Botey, A., Alvarez, L., Poch, E., Quintó, L., Saurina, A., et al., 2000 Jull. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. Am. J. Kidney Dis. [Internet] 36 (1), 29–34 [cited 2015 Jul 9].

Conroy, R.M., Pyörälä, K., Fitzgerald, A.P., Sans, S., Menotti, A., De Backer, G., et al., 2003 Junn. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur. Heart J. 24 (11), 987–1003.

Di Angelantonio, E., Chowdhury, R., Sarwar, N., Aspelund, T., Danesh, J., Gudnason, V., 2010 Sep 30. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. BMJ [Internet] 341 (sep30 1), c4986 [cited 2012 Oct 24].

Di Angelantonio, E., Danesh, J., Eiriksdottir, G., Gudnason, V., 2007 Sepp. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. PLoS Med. [Internet] 4 (9), e270 [cited 2012 Oct 24].

Donfrancesco, C., Palleschi, S., Palmieri, L., Rossi, B., Lo Noce, C., Pannozzo, F., et al., 2013. Estimated glomerular filtration rate, all-cause mortality and cardiovascular diseases incidence in a low risk population: the MATISS study. PLoS ONE 8 (3), e78475.

García-Gil, M.D.M., Hermosilla, E., Prieto-Alhambra, D., Fina, F., Rosell, M., Ramos, R., et al., 2011 Jann. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform. Prim. Care [Internet] 19 (3), 135–145 [cited 2013 Oct 10].

Gènova-Maleras, R., Catalá-López, F., de Larrea-Baz, N.F., Álvarez-Martín, E., Morant-Ginestar, C., 2011 Jann. The burden of premature mortality in Spain using standard expected years of life lost: a population-based study. BMC Public Health [Internet] 11(1). BioMed Central Ltd, p. 787 [cited 2012 Oct 24].

Go, A.S., Chertow, G.M., Fan, D., McCulloch, C.E., Hsu, C., 2004 Sep 23. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N. Engl. J. Med. [Internet] 351 (13), 1296–1305.

Graham, I., Atar, D., Borch-Johnsen, K., Boysen, G., Burell, G., Cifkova, R., et al., 2007 Sepp. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by R. Eur J Cardiovasc Prev Rehabil [Internet]. 14 Suppl 2, pp. E1–40 [cited 2013 Oct 24].

Group KDIGO (KDIGO) CW, 2013. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl [Internet] 3 (3), 1–150.

Hallan, S.I., Coresh, J., Astor, B.C., Asberg, A., Powe, N.R., Romundstad, S., et al., 2006 Augg. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J. Am. Soc. Nephrol. [Internet] 17 (8), 2275–2284 [cited 2015 Mar 11].

INE, 2014. Defunciones según la causa de muerte [Internet]. INE. [cited 2014 Aug 18].

Krishnan, E., Pandya, B.J., Ching, L., Dabbous, O., 2011. Hyperuricemia and the risk for subclinical coronary atherosclerosis - data from a prospective observational cohort study. Arthritis Research & Therapy 13, R66.

Lee, M., Saver, J.L., Chang, K.-H., Liao, H.-W., Chang, S.-C., Ovbiagele, B., 2010 Sep 30. Low glomerular filtration rate and risk of stroke: meta-analysis. BMJ [Internet] 341 (sep30 1), c4249 [cited 2012 Oct 24].

Levey, A.S., Stevens, L.A., Schmid, C.H., Zhang, Y.L., Castro, A.F., Feldman, H.I., et al., 2009 May 5. A new equation to estimate glomerular filtration rate. Ann. Intern. Med. [Internet] 150 (9), 604–612 [cited 2013 Jun 21].

Marrugat, J., Subirana, I., Comín, E., Cabezas, C., Vila, J., Elosua, R., et al., 2007 Jann. Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA Study. J. Epidemiol. Community Health [Internet] 61 (1), 40–47 [cited 2013 Oct 24].

Marrugat, J., Vila, J., Baena-Díez, J.M., Grau, M., Sala, J., Ramos, R., et al., 2011 Mayy. Relative validity of the 10-year cardiovascular risk estimate in a population cohort of the REGICOR study. Rev. Esp. Cardiol. (Engl Ed) [Internet] 64 (5), 385–394 [cited 2014 Oct 23].

Mathers, C.D., Loncar, D., 2006 Nov [cited 2014 Jul 9]. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. [Internet] 3 (11), e442.

Matsushita, K., Selvin, E., Bash, L.D., Astor, B.C., Coresh, J., 2010a. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the

MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. Am. J. Kidney. Dis. [Internet] 55 (4), 648–659 [cited 2012 Nov 22].
Matsushita, K., van der Velde, M., Astor, B.C., Woodward, M., Levey, A.S., de Jong, P.E., et al., 2010b. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet [Internet]. Elsevier Ltd 375 (9731), 2073–2081 [cited 2012 Oct 24].
Meisinger, C., Döring, A., Löwel, H., et al., 2006 Mayy. Eur. Heart J. [Internet] 27 (10), 1245–1250 [cited 2012 Oct 24].
Nakayama, M., Metoki, H., Terawaki, H., Ohkubo, T., Kikuya, M., Sato, T., et al., 2007 Jull. Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population–the Ohasama study. Nephrol. Dial. Transplant [Internet] 22 (7), 1910–1915 [cited 2015 Apr 2].
Nichols, M., Townsend, N., Luengo-Fernandez, R., Leal, J., Gray, A., Scarborough, P.R.M., 2012. European Cardiovascular Disease Statistics 2012 [Internet].
Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Z., Verschuren, M., et al., 2012 Jull. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Re. Eur Heart J [Internet]. 33(13) pp. 1635–1701 [cited 2013 May 23].
Perrone, D., Madias, N.E., A., L., 1992. Serum creatinine as an index of renal function: new insights into old concepts. Clin. Chem. 38 (10), 1933–1953.
Prieto-Alhambra, D., Judge, A., Javaid, M.K., Cooper, C., Diez-Perez, A., Arden, N.K., 2014 Sepp. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann. Rheum. Dis. [Internet] 73 (9), 1659–1664 [cited 2014 Sep 27].
Puddu, P.E., Bilancio, G., Terradura Vagnarelli, O., Lombardi, C., Mancini, M., Zanchetti, A., et al., 2014 Feb 15. Serum uric acid and eGFR_CKDEPI differently predict long-term cardiovascular events and all causes of deaths in a residential cohort. Int. J. Cardiol. 171 (3), 361–367.
Rabar, S., Harker, M., O'Flynn, N., Wierzbicki, A.S., 2014 Jann. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ [Internet] 349, g4356 [cited 2014 Oct 9].
Ramos, R., Balló, E., Marrugat, J., Elosua, R., Sala, J., Grau, M., et al., 2012 Jann. Validity for use in research on vascular diseases of the SIDIAP (Information System for the Development of Research in Primary Care): the EMMA study. Rev española Cardiol [Internet] 65 (1), 29–37 [cited 2012 Oct 24].
Rule, A., Teo, B., 2009 Junee. GFR estimation in Japan and China: what accounts for the difference? Am J Kidney Dis. 53 (6), 932–935.
Sambon, S., Maggi, S., Zanoni, S., Romanato, G., Noale, M., Corti, M.C., et al., 2012. Association of single measurement of estimated glomerular filtration rate and non-quantitative dipstick proteinuria with all-cause and cardiovascular mortality in the elderly. Results from the Progetto Veneto Anziani (Pro.V.A.) study. Atherosclerosis 220, 201–207.
Shara, N.M., Wang, H., Valaitis, E., Pehlivanova, M., Carter, E.A., HE, R., et al., 2011 Feb 1. Comparison of estimated glomerular filtration rates and albuminuria in predicting risk of coronary heart disease in a population with high prevalence of diabetes mellitus and renal disease. Am. J. Cardiol. [Internet]. Elsevier Inc. 107 (3), 399–405 [cited 2012 Oct 24].
Simó, R., Plana-Ripoll, O., Puente, D., Morros, R., Mundet, X., Vilca, L.M., et al., 2013 Jann. Impact of glucose-lowering agents on the risk of cancer in type 2 diabetic patients. The barcelona case-control study. PLoS One [Internet] 8 (11), e79968 [cited 2014 Sep 22].
Smink, P.A., Lambers Heerspink, H.J., Gansevoort, R.T., de Jong, P.E., Hillege, H.L., Bakker, S.J.L., et al., 2012 Novv. Albuminuria, estimated GFR, traditional risk factors, and incident cardiovascular disease: the PREVEND (Prevention of Renal and Vascular Endstage Disease) study. Am. J. Kidney. Dis. [Internet] 60 (5), 804–811 [cited 2013 Jul 11].
Team R Core, 2014. R: a language and environment for statistical computing. [Internet]. R Foundation for Statistical Computing, Vienna, Austria [cited 2014 Jan 1].
Van Biesen, W., De Bacquer, D., Verbeke, F., Delanghe, J., Lameire, N., Vanholder, R., 2007 Febb. The glomerular filtration rate in an apparently healthy population and its relation with cardiovascular mortality during 10 years. Eur. Heart J. [Internet] 28 (4), 478–483 [cited 2012 Nov 22].
Vinagre, I., Mata-Cases, M., Hermosilla, E., Morros, R., Fina, F., Rosell, M., et al., 2012 Aprr. Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). Diabetes Care [Internet] 35 (4), 774–779 [cited 2014 Oct 5].
Violán, C., Foguet-Boreu, Q., Hermosilla-Pérez, E., Valderas, J.M., Bolíbar, B., Fàbregas-Escurriola, M., et al., 2013 Jann. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. BMC Public Health [Internet] 13, 251 [cited 2014 Oct 14].
Wen, C.P., Cheng, T.Y.D., Tsai, M.K., Chang, Y.C., Chan, H.T., Tsai, S.P., et al., 2008 Jun 28. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. Lancet [Internet] 371 (9631), 2173–2182 [cited 2015 Apr 2].
White, I.R., Royston, P., Wood, A.M., 2011 Feb 20. Multiple imputation using chained equations: Issues and guidance for practice. Stat. Med. [Internet] 30 (4), 377–399 [cited 2014 Oct 9].
World Health Organization, 2011. Global status report on noncommunicable disaeses 2010 [Internet]. WHO. World Health Organization, Geneva [cited 2014 Jul 16].